

Final report-Teratologic Evaluation of FDA 71-65 (Ascorbic Acid) in Mice & Rat.

1/10/75

1FE

FROM



FOOD AND DRUG  
*Research* LABORATORIES, INC.

ROUTE 17C (P.O. BOX 107)  
WAVERLY, NEW YORK 14892

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FINAL

January 10, 1975

Teratologic Evaluation of FDA 71-65

(Ascorbic acid)

in

Mice and Rats



**FOOD AND DRUG**  
*Research* **LABORATORIES, INC.**

F I N A L  
R E P O R T

WAVERLY DIVISION  
Route 17  
P.O. Box 107  
Waverly, New York 14892  
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Submitted to: Department of Health, Education  
and Welfare  
Food and Drug Administration  
Negotiated Contracts Branch, HFA-510  
5600 Fishers Lane  
Rockville, Maryland 20852

Date: January 10, 1975  
Laboratory No. 2123 (15)  
Contract No. FDA 223-74-217

Sample: Very fine white powdered material

Marking: FDA 71-65 (Ascorbic acid)

Examination Requested: Teratologic evaluation of FDA 71-65 in mice.

Procedure: See Appendix I

Results: See Tables 1 through 5, Figure 1, and Appendix II

Conclusion: On the basis of the data presented herein, the following conclusion appears to be warranted:

"The administration of up to 520 mg/kg (body weight) of the test material to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

*David E. Bailey*  
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David E. Bailey, Ph.D.  
Director, Waverly Division

*Kenneth Morgareidge*  
\_\_\_\_\_  
Kenneth Morgareidge, Ph.D.  
Scientific Director

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 41 & 42; 47 through 50

Date: December 6, 1974

Material: FDA 71-65

Laboratory No.: 2123 (15)

Table 1

Fate Summary  
( Mice )

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant <sup>1</sup>
41	Sham	0.0	25	21	25	21
42	Aspirin*	150.0	27	20	27	20
47	FDA 71-65	5.2	25	23	25	23
48	FDA 71-65	24.1	30	20	30	20
49	FDA 71-65	112.0	25	20	25	20
50	FDA 71-65	520.0	25	23	25	23

\* Positive Control: 150.0 mg/kg

\*\* Administered as a water suspension (10 ml per kg of body weight); (See Appendix I)

1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 41 & 42; 47 through 50

Date: December 6, 1974

Table 2

Reproduction Data

Laboratory No. : 2123 (15)

Material : FDA 71-65

( Mice )

	Group:					
	41	42	47	48	49	50
Dose (mg/kg):	Sham	Aspirin**	5.2	24.1	112.0	520.0
Pregnancies						
Total No.	21	20	23	20	20	23
Died or Aborted (before Day 17)	0	0	0	0	0	0
To term (on Day 17)	21	20	23	20	20	23
Corpora Lutea						
Total No.	275	233	281	240	251	285
Average/dam mated	11.0	8.63	11.2	8.00	10.0	11.9
Live Litters						
Total No.*	21	20	23	20	19	23
Implant Sites						
Total No.	259	218	268	224	238	279
Average/dam*	12.3	10.9	11.7	11.2	11.9	12.1
Resorptions						
Total No.*	8	8	4	8	17	6
Dams with 1 or more sites resorbed	8	6	3	4	9	4
Dams with all sites resorbed	--	--	--	--	1	--
Per cent partial resorptions	38.1	30.0	13.0	20.0	45.0	17.4
Per cent complete resorptions	--	--	--	--	5.00	--
Live Fetuses						
Total No.	248	208	263	215	219	272
Average/dam*	11.8	10.4	11.4	10.8	11.0	11.8
Sex ratio (M/F)	1.04	0.84	0.80	0.78	1.02	0.89
Dead Fetuses						
Total No.*	3	2	1	1	2	1
Dams with 1 or more dead	3	1	1	1	2	1
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	14.3	5.00	4.35	5.00	10.0	4.35
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	0.80	0.85	0.82	0.83	0.82	0.87

\* Includes only those dams examined at term.

\*\* Positive Control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 41 & 42; 47 through 50

Laboratory No. 2123 (15)

Table 3

Material FDA 71-65

Date December 6, 1974

Summary of Skeletal Findings\*  
( Mice )

Findings	Group No. : Dose (mg/kg) :	41 Sham	42 Aspirin**	47 5.2	48 24.1	49 112.0	50 520.0
Live Fetuses Examined (at term)		173/21	144/20	182/23	148/20	153/19	190/23
Sternebrae							
Incomplete oss.		60/19	65/19	33/15	19/12	67/18	12/7
Scrambled							
Bipartite			1/1			1/1	1/1
Fused							
Extra							
Missing		39/12	36/11	27/8	12/6	24/11	3/2
Other							
Ribs							
Incomplete oss.							
Fused/split							
Wavy							
Less than 12							
More than 13		23/10	32/14	37/13	6/6	23/11	18/12
Other							
Vertebrae							
Incomplete oss.		4/2	11/5	9/4	2/2	6/5	1/1
Scrambled							
Fused							
Extra ctrs. oss.							
Scoliosis							
Tail defects							
Other							
Skull							
Incomplete closure		2/2		2/1			
Missing							
Craniostosis							
Other							
Extremities							
Incomplete oss.		6/4	15/5	6/3		3/3	
Missing							
Extra							
Miscellaneous							
Hyoid; missing		30/12	60/16	40/16	20/11	30/12	17/8
Hyoid; reduced		26/12	18/13	27/17	14/7	32/12	12/7

\* Numerator=Number of fetuses affected; Denominator=Number of litters affected.

\*\* Positive control: 150.0 mg/Kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 41 & 42; 47 through 50

Date December 6, 1974

Material FDA 71-65

Table 3-a

Laboratory No. 2123 (15)

Summary of Soft Tissue Abnormalities  
(Mice)

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Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
47	FDA 71-65	5.2	24401	1	Encephalomeningocele
50	FDA 71-65	520.0	24474	1	Umbilical hernia

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 41 & 42; 47 through 50

Date December 6, 1974

Table 4

Laboratory No. 2123 (15)

Species Mice

Average Body Weights\*

Group	Material	Dose Level	Day					17**
			0	6	11	15	15	
41	Sham	0.0	31	34	37	44	50 (21)	
42	Aspirin***	150.0	29	33	36	43	49 (20)	
47	FDA 71-65	5.2	28	32	35	42	48 (23)	
48	FDA 71-65	24.1	32	34	38	45	51 (20)	
49	FDA 71-65	112.0	31	34	37	43	49 (20)	
50	FDA 71-65	520.0	30	32	37	45	51 (23)	

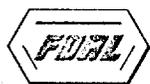
mg/kg

\* Of pregnant dams

\*\* Number of surviving dams in parentheses (c.f. Table 1)

\*\*\* Positive control: 150.0 mg/kg

Table 5



Groups 41 through 46

Laboratory No. 2123 (15)

Compound FDA 71-65

Species: Mice

## Daily Temperature and Humidity Record

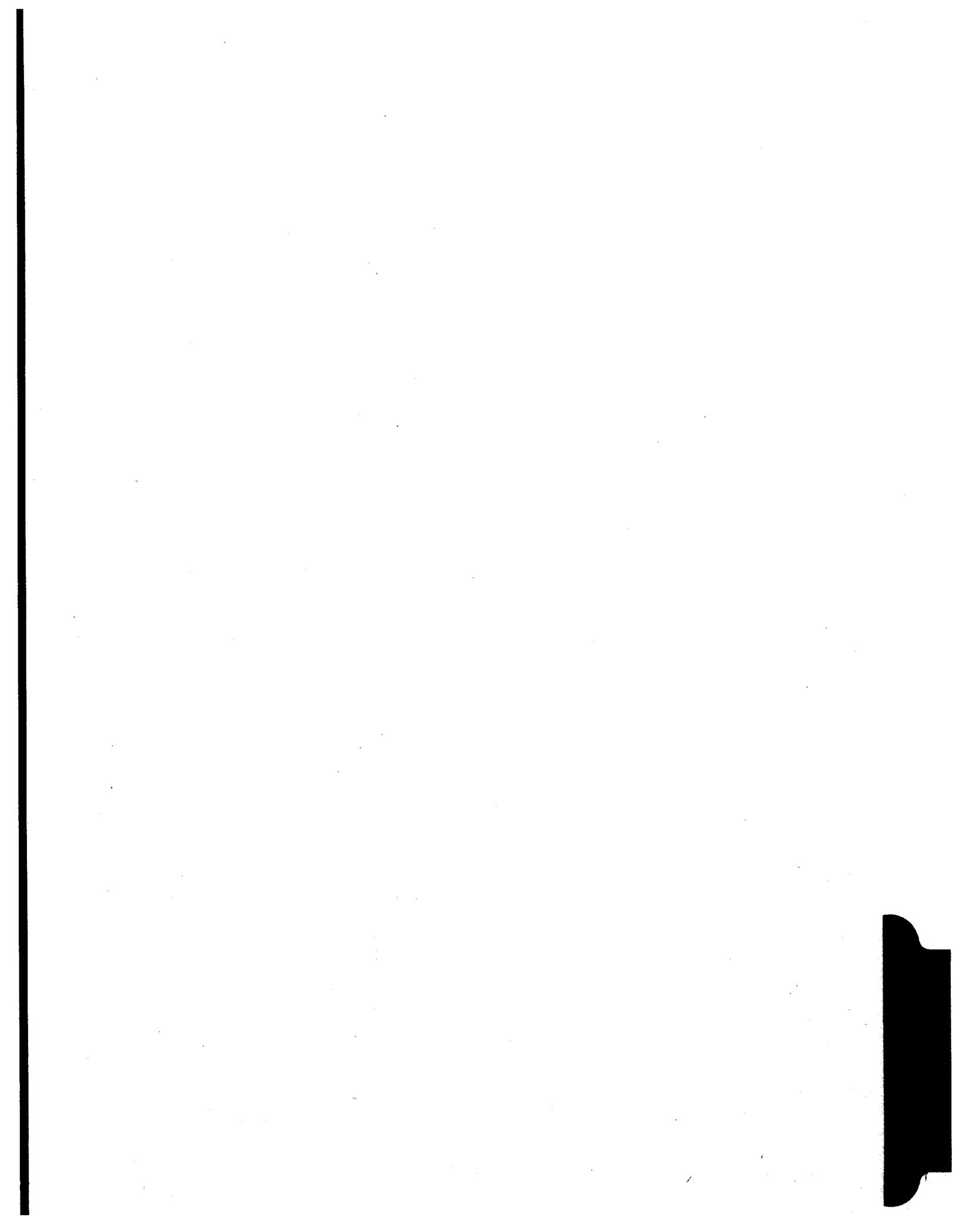
Date	Time	Temp	Relative Humidity
1974	a.m.	OF	%
10/6	8:00	76	65
10/7	8:15	75	65
10/8	8:45	70	62
10/9	8:30	70	62
10/10	8:45	74	71
10/11	8:10	72	62
10/12	8:00	74	65
10/13	9:00	74	64
10/14	7:30	76	63
10/15	8:45	76	74
10/16	8:45	71	70
10/17	8:00	76	60
10/18	9:30	76	60
10/19	9:00	74	47
10/20	1:00 p.m.	74	60
10/21	11:00	75	55
10/22	8:00	75	53
10/23	9:00	76	55
10/24	11:00	76	55
10/25	9:00	76	53
10/26	9:00	76	42
10/27	9:00	75	47
10/28	8:30	76	46
10/29	10:30	82	47
10/30	9:00	72	70
10/31	9:30	72	68
11/1	9:00	72	70
11/2	12:30	78	67



Figure 1

(Mice)

Photographs of Grossly Abnormal Fetuses  
in Test Group  
Inadvertently Omitted





## Appendix I

### Teratology Study in Mice

Virgin adult female albino CD-1 outbred mice were gang-housed in disposable plastic cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. (One male was not permitted to impregnate more than one female per group.) Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubation. The controls were sham treated with the vehicle at a level equivalent to the group receiving the highest dose.

Body weights were recorded on Days 0, 6, 11, 15, and 17 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal. Daily room temperature and humidity were recorded.

On Day 17 all dams were subjected to Caesarean section under surgical anesthesia, and the sex, numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing the Wilson technique. (Colored photographs were taken of all grossly abnormal



fetuses.) The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.



FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 41 Appendix II Date December 6, 1974  
 Material Sham Laboratory No. 2123  
 Dose 0.0 mg/kg Reproduction Data in Mice (Individual)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
24201	P	18	14	14		7	7		0.76	
24202	P	12	11	10		5**	4**	1	0.62	
24203	NP	0	0						---	
24204	P	13	12	11		5	6	1	0.76	
24205	P	15	15	14		5	9	1	0.63	
24206	NP	0	0						---	
24207	P	14	14	14		10	4		0.84	
24208	P	15	15	15		10	5		0.88	
24209	P	11	10	10		4	6		0.80	
24210	P	9	9	8		5	3	1	1.00	
24211	P	13	13	12		6	6	1	0.76	
24212	NP	0	0						---	
24213	NP	0	0						---	
24214	P	15	15	14	1	5	9		0.76	
24215	P	16	14	14		7	7		0.88	
24216	P	13	13	13		6	7		1.17	
24217	P	13	12	12		4	8		0.61	
24218	P	12	9	9		5	4		0.74	
24219	P	15	15	14		8	6	1	0.82	
24220	P	11	11	10		6	4	1	0.77	
24221	P	11	11	11		5	6		0.76	
24222	P	10	10	9	1	5	4		0.84	
24223	P	13	12	12		7	5		0.74	
24224	P	12	11	10	1	4	6		0.68	
24225	P	14	13	12		7	5	1	0.90	

\* P = Pregnant; NP = Not Pregnant

\*\* Not all Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 42

Appendix II

Date December 6, 1974

Material Aspirin

Reproduction Data in Mice (Individual)

Laboratory No. 2123

Dose 150.0 mg/kg

Dam No.	Fate*	Corpora		Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
		Lutea			Alive	Dead	M	F			
24231	P	11		10		7		3	4	3	0.65
23232	NP	0		0							---
24233	P	13		11		11		6	5		0.74
24234	NP	0		0							---
24235	P	13		13		12		6	6	1	0.82
24236	P	12		11		11		6	5		0.94
24237	NP	0		0							---
24238	P	12		10		9		5	4	1	0.96
24239	P	13		13		12		4	8	1	0.86
24240	P	13		12		12		7	5		1.00
24241	NP	0		0							---
24242	P	15		13		11	2	6	5		0.83
24243	P	11		11		11		2	9		0.52
24244	NP	0		0							---
24245	P	13		12		12		6	6		0.82
24246	NP	0		0							---
24247	P	10		9		9		6	3		0.87
24248	P	10		10		10		5	5		0.98
24249	NP	0		0							---
24250	P	14		13		13		7	6		0.81
24251	P	5		5		5		2	3		0.83
24252	P	11		10		10		3	7		0.96
24253	P	10		10		9		3	6	1	0.91
24254	P	10		9		8		4	4	1	1.17
24255	P	12		12		12		6	6		0.73
24256	P	15		15		15		6	9		0.86
24257	P	10		9		9		2	7		0.70

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 47

Appendix II

Date December 16, 1974

Material FDA 71-65

Reproduction Data in Mice (Individual)

Laboratory No. 2123 (15)

Dose 5.2 mg/kg

Dam No.	Fate*	Corpora		Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
		Lutea			Alive	Dead	M	F			
24381	P	12		12		12		5	7		0.57
24382	P	14		13		13		6	7		0.68
24383	P	11		11		11		3	8		0.77
24384	P	11		10		9		4	5	1	0.75
24385	P	12		12		12		6	6		0.51
24386	P	16		14		14		7	7		0.96
24387	P	12		11		10		4	6	1	1.00
24388	P	12		12		10		5	5	2	0.94
24389	NP	0		0							----
24390	P	9		9		9		3	6		0.89
24391	P	13		12		12		6	6		0.92
24392	P	13		12		12		4	8		0.84
24393	P	13		12		12		5	7		0.81
24394	P	12		12		12		5	7		0.73
24395	P	11		11		11		4	7		0.87
24396	NP	0		0							----
24397	P	10		10		10		5	5		0.91
24398	P	13		12		12		6	6		0.88
24399	P	12		11		10	1	7	3		0.80
24400	P	10		10		10		4	6		0.80
24401	P	15		14		14		8	6		0.91
24402	P	13		13		13		6	7		0.88
24403	P	13		12		12		4	8		0.84
24404	P	11		11		11		4	7		0.77
24405	P	13		12		12		6	6		0.88

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 48

Appendix II

Date December 6, 1974

Material FDA 71-65

Reproduction Data in Mice (Individual)

Laboratory No. 2123 (15)

Dose 24.1 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
24411	NP	0	0							
24412	P	14	13	13		6	7		0.84	
24413	P	16	15	15		7	8		0.80	
24414	P	13	13	12		5	7	1	0.82	
24415	NP	0	0							
24416	P	14	14	13	1	5	8		0.90	
24417	P	13	12	12		5	7		0.85	
24418	P	11	11	11		5	6		0.83	
24419	P	10	8	5		2	3	3	0.78	
24420	P	13	13	11		5	6	2	0.74	
24421	P	12	12	12		4	8		0.84	
24422	P	10	9	7		3	4	2	0.95	
24423	NP	0	0							
24424	NP	0	0							
24425	NP	0	0							
24426	P	12	10	10		5	5		0.95	
24427	P	15	14	14		7	7		0.77	
24428	P	14	12	12		6	6		0.79	
24429	P	12	12	12		5	7		0.77	
24430	NP	0	0							
24431	NP	0	0							
24432	NP	0	0							
24433	P	7	6	6		2	4		1.08	
24434	P	9	9	9		3	6		0.78	
24435	P	13	11	11		5	6		0.76	
24436	P	9	8	8		4	4		0.80	
24437	P	14	13	13		6	7		0.83	
24438	NP	0	0							
24439	P	9	9	9		4	5		0.77	
24440	NP	0	0							

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 49 Date December 6, 1974  
 Material FDA 71-65 Appendix II  
 Dose 112.0 mg/kg Laboratory No. 2123 (15)  
 Reproduction Data in Mice (Individual)

Dam No.	Fate*	Corpora		Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
		Lutea	Implant Sites	Alive	Dead	M	F			
24441	P	9	7					7	-----	
24442	P	14	14	14		5	9		0.76	
24443	P	13	13	13		7	6		0.88	
24444	P	12	12	12		7	5		0.82	
24445	P	13	11	11		5	6		0.89	
24446	P	12	11	9	1	5	4	1	0.80	
24447	NP	0	0						-----	
24448	NP	0	0						-----	
24449	P	15	15	13		8	5	2	0.78	
24450	P	14	13	12		6	6	1	0.87	
24451	P	13	12	11		6	5	1	0.92	
24452	NP	0	0						-----	
24453	P	13	13	13		7	6		0.79	
24454	NP	0	0						-----	
24455	P	17	17	17		7	10		0.95	
24456	P	14	13	13		7	6		0.90	
24457	P	13	13	11		4	7	2	0.67	
24458	P	12	12	11		8	3	1	0.87	
24459	P	11	9	8		5	3	1	0.86	
24460	P	7	7	7		5	2		0.84	
24461	P	11	10	9	1	3	6		0.79	
24462	P	15	14	14		6	8		0.70	
24463	P	14	14	13		6	7	1	0.75	
24464	NP	0	0						-----	
24465	P	9	8	8		4	4		0.83	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 50

Appendix II

Date December 6, 1974

Material FDA 71-65

Reproduction Data in Mice (Individual)

Laboratory No. 2123 (15)

Dose 520.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
24471	P	13	11	10		4	6	1	0.93	
24472	P	14	14	14		6	8		0.87	
24473	P	14	13	11		4	7	2	0.80	
24474	P	13	13	13		4	9		0.86	
24475	P	12	12	12		5	7		0.82	
24476	P	14	14	14		8	6		0.88	
24477	P	10	10	10		6	4		0.98	
24478	P	14	14	14		7	7		0.86	
24479	P	14	12	10		6	4	2	0.85	
24480	P	12	11	11		6	5		0.96	
24481	P	13	13	13		7	6		0.90	
24482	P	15	15	15		10	5		0.97	
24483	P	11	11	11		6	5		0.87	
24484	NP	0	0						----	
24485	P	14	14	14		5	9		0.72	
24486	P	11	10	9	1	6	3		0.85	
24487	P	13	10	10		5	5		0.91	
24488	P	12	12	12		5	7		0.81	
24489	P	13	13	13		5	8		0.79	
24490	P	14	13	13		5	8		0.84	
24491	P	16	14	14		6	8		0.92	
24492	NP	0	0						----	
24493	P	11	11	11		4	7		0.77	
24494	P	---	10	9		4	5	1	0.91	
24495	P	12	9	9		4	5		1.05	

\* P = Pregnant; NP = Not Pregnant

\*\* Not Recorded

RATS



**FOOD AND DRUG**  
*Research* **LABORATORIES, INC.**

F I N A L  
R E P O R T

WAVERLY DIVISION  
Route 17  
P.O. Box 107  
Waverly, New York 14892  
(607) 565-2931

Submitted to: Department of Health, Education  
and Welfare  
Food and Drug Administration  
Negotiated Contracts Branch, HFA-510  
5600 Fishers Lane  
Rockville, Maryland 20852

Date: January 10, 1975

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Conclusion: On the basis of the data presented herein, the following  
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"The administration of up to 550 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 41 & 42; 47 through 50

Date: December 6, 1974

Material: FDA 71-65

Laboratory No.: 2143 (15)

Table 1

Fate Summary  
( Rats )

Group	Material	Dose** mg/kg	Mated	Total		Surviving at Term	
				Pregnant	Total	Total	Pregnant <sup>1</sup>
41	Sham	0.0	21	20	21	20	20
42	Aspirin*	250.0	21	20	21	20	20
47	FDA 71-65	5.5	22	20	22	20	20
48	FDA 71-65	25.5	21	20	21	20	20
49	FDA 71-65	118.5	20	20	20	20	20
50	FDA 71-65	550.0	21	20	21	20	20

\* Positive Control: 250.0 mg/kg

\*\* Administered as a water suspension (See Appendix I)

1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 41 & 42; 47 through 50  
 Material: FDA 71-65

Table 2  
 Reproduction Data  
 ( Rats )  
 Date: December 6, 1974  
 Laboratory No.: 2143 (15)

	41	42	47	48	49	50
Group:	41	42	47	48	49	50
Dose (mg/kg):	Sham	Aspirin**	5.5	25.5	118.5	550.0
Pregnancies						
Total No.	20	20	20	20	20	20
Died or Aborted (before Day 20)	0	0	0	0	0	0
To term (on Day 20)	20	20	20	20	20	20
Corpora Lutea						
Total No.	267	263	254	283	254	254
Average/dam mated	12.7	12.5	11.6	13.5	12.7	12.1
Live Litters						
Total No.*	20	19	20	20	20	20
Implant Sites						
Total No.	262	238	221	265	231	239
Average/dam*	13.1	11.9	11.1	13.3	11.6	12.0
Resorptions						
Total No.*	--	35	9	--	4	1
Dams with 1 or more sites resorbed	--	7	7	--	3	1
Dams with all sites resorbed	--	1	--	--	--	--
Per cent partial resorptions	--	35.0	35.0	--	15.0	5.00
Per cent complete resorptions	--	5.00	--	--	--	--
Live Fetuses						
Total No.	262	203	212	265	227	238
Average/dam*	13.1	10.2	10.6	13.3	11.4	11.9
Sex ratio (M/F)	1.06	0.92	1.12	1.17	0.92	1.11
Dead Fetuses						
Total No.*	--	--	--	--	--	--
Dams with 1 or more dead	--	--	--	--	--	--
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	--	--	--	--	--	--
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	3.93	2.92	3.89	3.96	3.95	3.93

\* Includes only those dams examined at term.  
 \*\* Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 41 & 42; 47 through 50

Laboratory No. 2143 (15)

Table 3

Material FDA 71-65

Date December 6, 1974

Summary of Skeletal Findings\*  
( Rats )

Findings	Group No. : Dose (mg/kg) :	41 Sham	42 Aspirin**	47 5.5	48 25.5	49 118.5	50 550.0
Live Fetuses Examined (at term)		179/20	143/19	149/20	183/20	158/20	168/20
<b>Sternebrae</b>							
Incomplete oss.		37/16	89/19	44/16	50/16	45/15	41/13
Scrambled							
Bipartite			8/6	1/1			1/1
Fused							1/1
Extra							
Missing		3/3	70/15	2/2		9/3	2/2
Other							
<b>Ribs</b>							
Incomplete oss.		2/2	15/8	2/2	4/3		5/2
Fused/split			5/2				
Wavy		23/8	60/17	27/10	32/10	9/7	24/8
Less than 12							
More than 13		2/2	59/15	2/2			2/2
Other							
<b>Vertebrae</b>							
Incomplete oss.		4/4	68/18	15/6	12/5		11/4
Scrambled							
Fused							
Extra ctrs. oss.			1/1				
Scoliosis							
Tail defects							
Other							
<b>Skull</b>							
Incomplete closure		38/13	88/19	44/12	46/14	19/11	57/12
Missing							
Craniostosis							
Other							
<b>Extremities</b>							
Incomplete oss.			3/3				2/2
Missing							
Extra							
<b>Miscellaneous</b>							
Hyoid; missing		21/10	54/16	19/8	19/8	26/9	10/8
Hyoid; reduced		26/13	21/10	23/11	55/18	32/14	47/13

\* Numerator=Number of fetuses affected; Denominator=Number of litters affected.

\*\* Positive control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 41 & 42; 47 through 50

Date December 6, 1974

Material FDA 71-65

Laboratory No. 2143 (15)

Table 3-a

Summary of Soft Tissue Abnormalities  
(Rats)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
42	Aspirin*	250.0	44235	1	Hydrocephalus
			44240	1	Hydrocephalus; Encephalomeningocele
			44246	2	Hydrocephalus
			44252	1	Spina bifida; Encephalomeningocele
			44255	1	Hydrocephalus

\*Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 41 & 42: 47 through 50

Date December 6, 1974

Table 4

Laboratory No. 2143 (15)

Species Rats

Average Body Weights\*

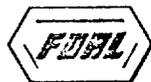
Group	Material	Dose Level	Day				
			0	6	11	15	
						20**	
		mg/kg					
41	Sham	0.0	226	248	263	286	359 (20)
42	Aspirin***	250.0	234	243	255	276	333 (20)
47	FDA 71-65	5.5	232	251	266	287	351 (20)
48	FDA 71-65	25.5	231	251	266	289	366 (20)
49	FDA 71-65	118.5	213	234	250	268	336 (20)
50	FDA 71-65	550.0	232	251	263	286	353 (20)

\* Of pregnant dams

\*\* Number of surviving dams in parentheses (c.f. Table 1)

\*\*\* Positive control: 250.0 mg/kg

Table 5



Groups 41 & 42; 47 through 50  
Compound FDA 71-65

Laboratory No. 2143 (15)

Species: Rats

Daily Temperature and Humidity Record

Date	Time	Temp	Relative Humidity
1974	a.m.	OF	%
9/27	8:20	72	65
9/28	8:30	76	70
9/29	8:15	74	76
9/30	8:20	72	65
10/1	8:30	72	65
10/2	9:30	70	63
10/3	10:00	68	64
10/4	9:00	70	63
10/5	10:30	74	65
10/6	8:00	76	65
10/7	8:15	75	65
10/8	8:45	70	62
10/9	8:30	70	62
10/10	8:45	74	71
10/11	8:10	72	62
10/12	8:00	74	65
10/13	9:00	74	64
10/14	7:30	76	63
10/15	8:45	76	74
10/16	8:45	71	70
10/17	8:00	76	60
10/18	9:30	76	60
10/19	9:00	74	47
10/20	1:00 p.m.	74	60
10/21	11:00	75	55
10/22	8:00	75	53
10/23	9:00	76	55
10/24	11:00	76	55
10/25	9:00	76	53
10/26	9:00	76	42
10/27	9:00	75	47
10/28	8:30	76	46
10/29	10:30	82	47



Figure 1

Photographs of Grossly Abnormal Fetuses

(None Observed in Test Groups)





Appendix I  
Teratology Study in Rats

Virgin adult female albino rats (Wistar derived stock) were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. (One male was not permitted to impregnate more than one female per group.) Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubations. The controls were sham treated with the vehicle at a level equivalent to the group receiving the highest test dose. The test material was prepared and doses calculated according to the following table:

<u>Dosage</u> (mg/kg)	<u>Dose</u> (ml/kg)	<u>Concentration</u> (mg/ml)
≤ 250	1	≤ 250
251-500	2	125-250
501-750	3	133-250
751-1000	4	187-250
1001-1600	5	200-250

Body weights were recorded on Days 0, 6, 11, 15 and 20 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal. Daily room temperature and humidity were recorded.



On Day 20 all dams were subjected to Caesarean Section under surgical anesthesia, and the sex, numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing the Wilson technique. (Colored photographs were taken of all grossly abnormal fetuses.) The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.



FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 41

Appendix II

Date December 6, 1974

Material Sham

Reproduction Data in Rats

(Individual)

Laboratory No. 2143

Dose 0.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
44201	P	15	15	15		9	6		4.03	
44202	P	15	15	15		9	6		3.81	
44203	P	6**	12	12		6	6		3.91	
44204	P	15	15	15		6	9		3.80	
44205	P	14	13	13		8	5		3.94	
44206	P	12	11	11		6	5		3.93	
44207	P	15	15	15		7	8		3.88	
44208	P	15	15	15		7	8		4.12	
44209	P	17	16	16		9	7		3.87	
44210	P	10	10	10		5	5		3.72	
44211	P	12	12	12		9	3		3.65	
44212	P	15	13	13		10	3		3.75	
44213	P	13	13	13		6	7		4.03	
44214	P	11	10	10		4	6		4.15	
44215	P	11	10	10		5	5		3.77	
44216	P	16	16	16		6	10		4.12	
44217	P	15	13	13		7	6		4.30	
44218	P	14	12	12		6	6		4.05	
44219	NP	0	0						-----	
44220	P	14	14	14		6	8		4.08	
44221	P	12	12	12		4	8		3.73	

\* P = Pregnant; NP = Not Pregnant

\*\* One Ovary Missing

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 42

Appendix II

Date December 6, 1974

Material Aspirin

Reproduction Data in Rats (Individual)

Laboratory No. 2143

Dose 250.0 mg/kg

Dam No.	Fate*	Corpora		Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
		Uterus	Uterus		Alive	Dead	M	F			
44231	P	15	14	14	14	9	5			2.97	
44232	P	13	13	13	13	7	6			3.63	
44233	P	10	10	10	10			10		----	
44234	P	13	11	11	10	2	8	1		2.91	
44235	P	15	14	14	10	5	5	4		2.57	
44236	P	11	10	10	10	5	5			3.12	
44237	P	11	9	9	4	2	2	5		2.97	
44238	P	14	13	13	13	5	8			2.82	
44239	P	14	14	14	14	6	8			2.96	
44240	P	16	15	15	15	5	10			2.90	
44241	P	15	14	14	14	7	7			2.74	
44242	P	14	14	14	14	7	7			3.20	
44243	NP	0	0	0						----	
44244	P	15	12	12	12	4	8			3.35	
44245	P	14	13	13	13	7	6			4.50	
44246	P	14	7	7	6	3	3	1		3.35	
44247	P	15	14	14	1	0	1	13		1.90	
44248	P	12	11	11	11	8	3			2.41	
44249	P	12	11	11	10	4	6	1		2.41	
44251	P	9	8	8	8	5	3			2.56	
44252	P	11	11	11	11	6	5			2.15	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 47

Appendix II

Date December 6, 1974

Material FDA 71-65

Reproduction Data in Rats (Individual)

Laboratory No. 2143 (15)

Dose 5.5 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
44381	P	15	14	13		3	10	1	4.09	
44382	P	12	11	11		6	5		4.11	
44383	P	16	15	14		11	3	1	3.84	
44384	NP	0	0						----	
44385	P	13	11	9		7	2	2	3.56	
44386	P	15	15	15		7	8		3.66	
44387	P	12	12	12		6	6		3.71	
44388	P	12	11	11		7	4		4.22	
44389	P	12	12	11		3	8	1	4.07	
44390	P	14	14	14		7	7		3.79	
44391	P	15	12	12		10	2		3.79	
44392	P	11	8	8		3	5		4.33	
44393	P	12	11	11		6	5		3.99	
44394	P	9	9	7		3	4	2	3.72	
44395	P	13	13	13		8	5		3.78	
44396	P	14	10	10		5	5		3.84	
44397	P	11	11	11		5	6		3.66	
44398	NP	0	0						----	
44399	P	11	6	6		2	4		3.81	
44400	P	11	3	2		2	0	1	4.37	
44401	P	15	14	13		6	7	1	3.57	
44402	P	11	9	9		5	4		3.98	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 48

Appendix II

Date December 6, 1974

Material FDA 71-65

Reproduction Data in Rats (Individual)

Laboratory No. 2143 (15)

Dose 25.5 mg/kg

Dam No.	Fate*	Corpora		Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
		Lutea	0		Alive	Dead	M	F			
44411	NP	0	0	0						----	
44412	P	15	15	15		15		8	7	4.03	
44413	P	14	14	14		14		8	6	3.57	
44414	P	13	12	12		12		6	6	4.19	
44415	P	12	11	11		11		6	5	3.80	
44416	P	12	12	12		12		9	3	3.96	
44417	P	13	13	13		13		12	1	4.11	
44418	P	13	11	11		11		5	6	3.99	
44419	P	13	13	13		13		6	7	4.32	
44420	P	16	15	15		15		9	6	3.60	
44421	P	16	14	14		14		8	6	3.94	
44422	P	14	13	13		13		7	6	3.92	
44423	P	14	12	12		12		6	6	3.83	
44424	P	15	12	12		12		7	5	3.68	
44425	P	16	15	15		15		8	7	3.96	
44426	P	17	17	17		17		9	8	4.03	
44427	P	15	14	14		14		8	6	4.05	
44428	P	13	11	11		11		3	8	4.00	
44429	P	12	12	12		12		8	4	4.04	
44430	P	17	16	16		16		4	12	4.25	
44431	P	13	13	13		13		6	7	3.85	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 49

Appendix II

Date December 6, 1974

Material FDA 71-65

Reproduction Data in Rats (Individual)

Laboratory No. 2143 (15)

Dose 118.5 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
44441	P	12	11	11		6	5		3.56	
44442	P	12	11	10		4	6	1	4.36	
44443	P	11	11	11		7	4		4.14	
44444	P	13	13	13		7	6		4.06	
44445	P	15	13	13		6	7		3.90	
44446	P	11	7	7		6	1		4.04	
44447	P	15	15	15		7	8		3.60	
44448	P	12	12	12		5	7		3.79	
44449	P	17	17	17		7	10		3.94	
44450	P	13	13	12		6	6	1	4.09	
44451	P	12	10	10		4	6		3.95	
44452	P	14	10	10		3	7		3.70	
44453	P	14	14	14		8	6		4.02	
44454	P	10	10	8		5	3	2	3.91	
44455	P	13	13	13		5	8		4.11	
44456	P	11	6	6		4	2		4.27	
44457	P	12	12	12		7	5		3.86	
44458	P	12	11	11		5	6		4.22	
44459	P	15	13	13		5	8		3.87	
44460	P	10	9	9		2	7		3.60	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 50

Appendix II

Date December 6, 1974

Material FDA 71-65

Reproduction Data in Rats (Individual)

Laboratory No. 2143 (15)

Dose 550.0 mg/kg

Dam No.	Fate*	Corpora lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
44471	P	14	14	14		8	6		3.79	
44472	P	10	10	10		9	1		3.87	
44473	P	12	11	11		4	7		3.93	
44474	P	14	14	14		3	11		3.95	
44475	P	13	12	12		7	5		3.82	
44476	P	15	15	15		6	9		3.59	
44477	P	13	11	11		4	7		3.72	
44478	P	16	14	14		10	4		4.39	
44479	P	18	18	18		12	6		3.93	
44480	P	14	14	14		8	6		3.52	
44481	P	15	14	14		8	6		3.47	
44482	P	13	13	13		8	5		3.78	
44483	P	11	10	9		5	4	1	4.34	
44484	P	12	10	10		4	6		4.04	
44485	P	12	11	11		5	6		4.00	
44486	P	5	4	4		2	2		4.39	
44487	P	13	13	13		7	6		3.84	
44488	P	7	4	4		2	2		4.41	
44489	P	13	13	13		7	6		4.16	
44490	NP	0	0						-----	
44492	P	14	14	14		6	8		3.61	

\* P = Pregnant; NP = Not Pregnant